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- (74) Agents: **INSOGNA, Anthony, M. et al.**; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).
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(54) Title: MODULATION OF STEM AND PROGENITOR CELL DIFFERENTIATION, ASSAYS, AND USES THEREOF

(57) Abstract: The present invention relates to methods of modulating mammalian stem cell and progenitor cell differentiation. The methods of the invention can be employed to regulate and control the differentiation and maturation of mammalian, particularly human stem cells along specific cell and tissue lineages. The methods of the invention relate to the use of certain small organic molecules to modulate the differentiation of stem or progenitor cell populations along specific cell and tissue lineages, and in particular, to the differentiation of embryonic-like stem cells originating from a postpartum placenta or for the differentiation of early progenitor cells to a granulocytic lineage. Finally, the invention relates to the use of such differentiated stem or progenitor cells in transplantation and other medical treatments.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/11190

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 65/00; C12N 5/00

US CL : 424/93.7; 435/377

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.7; 435/377

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, WPIDS, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,322,784 B1 (PITTINGER et al.) 27 November 2001 (27.11.2001), abstract, claim 5, examples.	1, 5, 7, 8, 25-30, 46
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Y		
X	WO 01/93909 A2 (GLAXO GROUP LIMITED) 13 December 2001 (13.12.2001), abstract, pages 4-6, claim 54	1-3, 5-8
X	SMITH et al. Expansion of Neutrophil Precursors and Progenitors in Suspension Cultures of CD34+ Cells Enriched from Human Bone Marrow. Experimental Hematology. 1993, Vol. 21, No. 7, pages 870-877, see abstract.	25, 26, 28-33



Further documents are listed in the continuation of Box C.



See patent family annex.

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/11190

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 4 and 27
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 4 and 27 use the trademark "SelCID". It is unclear what compound or compounds are meant by this recitation.
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-3, 5-8, 25, 26, 28-33, 46-49

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/11190

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-8, 25-33 and 46-49, drawn to a first method, a method of modulating the differentiation of a stem cell, the differentiated stem cell which is a product of the first method, and a method of use of the product, which is a differentiated stem cell.

Group II claims 9-16, drawn to a second method, a method of modulating the proliferation or of a CD34+ or CD133+ progenitor cell.

Group III, claims 17-24, drawn to a third method, a method of expanding a population of progenitor cells in a mammalian subject.

Group IV, claims 34-41, drawn to a second composition comprising isolated cord and white cells.

Group V, claims 42-45, drawn to a third composition comprising CD34+ or CD133+ progenitor cells.

Group VI, claims 50-53, drawn to a fourth method, a method of transplanting mammalian progenitor cells.

Group VII, claims 54-56, drawn to a fifth method, a method of treating an individual experiencing a condition.

Group VIII, claims 57-70, drawn to a sixth method, a method of treating an individual comprising administering white blood cells.

Group IX, claims 71-79, drawn to a seventh method, a method of making a composition comprising contacting CD34+ or CD133+ progenitor cells with the claim specific compound.

Group X, claim 80, drawn to a product of the process of Group IX.

Group XI, claims 81-89 and 101, drawn to an eighth method, a method of modulating the differentiation of CD34+ or CD133+ progenitor cells.

Group XII, claims 90-100, drawn to a ninth method, a method of producing differentiated cells from CD34+ progenitor cells.

The inventions listed as Groups I-XII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to a permissible category of inventions, namely a product, a process specially adapted for the manufacture of said product and a use of said product. Other methods and products are placed in their own group as PCT Rule 13.2 does not provide for multiple methods or products in a single category.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/11190

A. CLASSIFICATION OF SUBJECT MATTER

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US CL : 424/93.7; 435/377

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X — Y	US 6,322,784 B1 (PITTINGER et al.) 27 November 2001 (27.11.2001), abstract, column 3, line 37, claim 5, examples.	1,5,7-10,12,15,25-26, 28-30,46,50,53 16,47
X — Y	WO 01/93909 A2 (GLAXO GROUP LIMITED) 13 December 2001 (13.12.2001), abstract, pages 4-6, claim 54.	1-3, 5-10, 12-15 16
X — Y	SMITH et al. Expansion of Neutrophil Precursors and Progenitors in Suspension Cultures of CD34+ Cells Enriched from Human Bone Marrow. Experimental Hematology. 1993, Vol. 21, No. 7, pages 870-877, see Abstract, Materials and methods and Figures.	25, 26, 28-33, 42-44, 71-73, 75, 81-88 50-53



Further documents are listed in the continuation of Box C.



See patent family annex..

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

06 August 2004 (06.08.2004)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/11190

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because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 4,11,27,45,74,77-80 and 89-101
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
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3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☒

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/T1190

Continuation of Box I Reason 2:

the claims use the trademark "SelCID" relating to the use of compounds to differentiate cells. No specific definition or structure for this term is found in the description, rather merely a functional definition "small molecule drugs which are not peptides, proteins, nucleic acids, oligosaccharides or other macromolecules" on page 25. It is, therefore unclear what compounds are encompassed by this trademark, thus no meaningful search can be carried out.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-3, 5-8, 25-26, 28-33 and 46-49, drawn to a first method, a method of modulating the differentiation of a stem cell, the differentiated stem cell which is a product of the first method, and a method of use of the product, which is a differentiated stem cell.

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Group VIII, claims 57-70, drawn to a sixth method, a method of treating an individual comprising administering white blood cells.

Group IX, claims 71-73, 57-76, drawn to a seventh method, a method of making a composition comprising contacting CD34+ or CD133+ progenitor cells with the claim specific compound.

Group X, claims 81-88, drawn to an eighth method, a method of modulating the differentiation of CD34+ or CD133+ progenitor cells.

The inventions listed as Groups I-X do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I is directed to a permissible category of inventions, namely a product, a process specially adapted for the manufacture of said product and a use of said product. Other methods and products are placed in their own group as PCT Rule 13.2 does not provide for multiple methods or products in a single category.